PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference PRD2172-PCT	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2004/053280	International filing date *(day/month/year)* 06 December 2004 (06.12.2004)	Priority date *(day/month/year)* 09 December 2003 (09.12.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant JANSSEN PHARMACEUTICA N.V.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

   - ☒ Box No. I — Basis of the report
   - ☐ Box No. II — Priority
   - ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☒ Box No. IV — Lack of unity of invention
   - ☒ Box No. V — Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI — Certain documents cited
   - ☐ Box No. VII — Certain defects in the international application
   - ☐ Box No. VIII — Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 12 June 2006 (12.06.2006)
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Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/053280	06.12.2004	09.12.2003

International Patent Classification (IPC) or both national classification and IPC
C07D211/60, C07D211/34, C07D405/12, C07D401/12, A61K31/445, A61P3/06

Applicant
JANSSEN PHARMACEUTICA N.V.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations

   see separate sheet

Reference is made to the following documents:

D1: WO-A-02081460
D2: WO-A-03048121

Re Item IV

The International Searching Authority found multiple (groups of) inventions in this international application, the reasons being the following:

D1 discloses lipid lowering biphenylcarboxamides. The generic formula (I) of D1 (cf. claim 1) overlaps with the present claim 1 whereas the proviso of D1 relating to the definition of radical A excludes the possibility that A is a bond (or unsubstituted alkanediyl) when Z is of formula (a-5).

The present compounds differ from the compounds of D1 in that they are excluded from the scope of claim 1 of D1 by the said proviso.

The technical problem underlying the present application is seen in the provision of alternative lipid lowering compounds.

In view of the variability of the residue -Z-A-CO-B as defined in D1 the skilled person would assume that the said proviso does not exclude inactive compounds but was introduced for excluding prior art compounds. Therefore, D1 prompts the skilled person faced with the above mentioned problem to apply the compounds excluded by the proviso of D1 as lipid lowering agents.

Furthermore, the document D2 discloses related lipid lowering agents comprising an acetyl substituted piperazine ring (closely related to the compounds of D1 which are excluded by the proviso, cf. claim 1 of D2 and example 44). Consequently, the document D2 prompts the skilled in the art faced with the above mentioned problem to use the compounds excluded by the proviso of D1 as lipid lowering agents. Therefore, the different groups of compounds according to present claims 1 do not share a common special technical feature as required by Rule 13.2 PCT, and the present application lacks unity of invention

(Rule 13.1 PCT).

The following groups of inventions were detected:

1. Compounds according to claim 1 in which n is 0.
2. Compounds according to claim 1 in which n is 1.

Re Item V

First invention

1) The subject-matter of present claims 1, 2 and 7-10 is new (Article 33(2) PCT).

The generic formula (I) of D1 (cf. claim 1) overlaps with the present claim 1 whereas the proviso of D1 requires that when Z is of formula (a-5) then A is a C_{1-6} alkanediyl substituted with aryl, heteroaryl or cycloalkyl.
The subject-matter of the present claims is regarded as novel selection from the disclosure of D1.

2) The subject-matter of claims 1, 2 and 7-10 does not involve an inventive step (Article 33(3) PCT).

D1 discloses lipid lowering biphenylcarboxamides. The generic definition of formula (I) of D1 (cf. claim 1) overlaps with the present claim 1 whereas the proviso of D1 relating to the definition of radical A excludes the possibility that A is a bond when Z is of formula (a-5). Furthermore, the document relates to compounds in which Z is of formula (a-1) and A is a bond (p4 is 0, X1 is CH, X2 is N, n is 2, R5 and R6 are methyl, and B is of formula (b-1) or (b-3)) or to compounds in which Z is of formula (a-3) and A is a bond (p4 is 0, X1 is CH, m is 1, and B is of formula (b-1) or (b-3)).
The present compounds differ from the compounds of D1 in that they comprise a group Z of formula (a-5) [piperidine] when A is a bond which is excluded from the scope of claim 1 of D1 by the proviso.

The technical problem underlying the present application is seen in the provision of alternative lipid lowering compounds.
The application does not comprise test data showing that the problem is actually solved by the present compounds in which n is 0. In view of the fact that the document D2 (cf. below), disclosing closely related compounds, also not comprises test data, it can not be decided whether the claimed compounds solve the technical problem or not.

In case the problem is solved, the solution does not involve an inventive step for the following reasons:

a) In view of the variability of the residue -Z-A-CO-B as defined in D1 the skilled person would assume that the said proviso does not exclude inactive compounds but was introduced for excluding prior art compounds. Therefore, D1 alone prompts the skilled person faced with the above mentioned problem to apply the compounds excluded by the proviso of D1 as lipid lowering agents.

b) The document D2 discloses further related lipid lowering agents comprising an acetyl substituted piperazine ring (closely related to the compounds excluded from the scope of D1 by proviso, cf claim 1 of D2 and example 44).
Consequently, the document D2 prompts the skilled in the art faced with the above mentioned problem to use the compounds excluded by the proviso of D1 as lipid lowering agents. These compounds fall within the present claim 1 which, therefore, does not involve inventive activity.

Inventive activity could only be acknowledged if the claimed compounds exhibited unexpected effects or properties in relation to the closest compounds of D1 (cf. above).

Second invention

1) The subject-matter of present claims 1-10 is new (Article 33(2) PCT).

The present compounds comprise a residue $-(CH_2)_1-C(O)-Y-R_1$ whereas the

corresponding -(CH_2)-group in the compounds of D1 is substituted (cf. proviso in claim 1 of D1).

2) The subject-matter of claims 1-10 does not involve an inventive step (Article 56 EPC).

D1 discloses lipid lowering biphenylcarboxamides. The generic definition of formula (I) of D1 (cf. claim 1) overlaps with the present claim 1 whereas the proviso of D1 relating to the definition of radical A excludes the possibility that A is unsubstituted alkylene when Z is of formula (a-5). Furthermore, the document relates to compounds in which Z is of formula (a-1) and A is alkylene (p4 is 0, X1 is CH, X2 is N, n is 2, R5 and R6 are methyl, and B is of formula (b-1) or (b-3)) or to compounds in which Z is of formula (a-3) and A is alkylene (p4 is 0, X1 is CH, m is 1, and B is of formula (b-1) or (b-3)).

The present compounds differ from the compounds of D1 in that they comprise a group Z of formula (a-5) [piperidine] when A is unsubstituted alkylene which is excluded from the scope of claim 1 of D1 by the proviso.

The technical problem underlying the present application is seen in the provision of alternative lipid lowering compounds.

In view of the test data disclosed on the pages 25-27, the problem appears to be solved.

The document D2 discloses further related lipid lowering agents comprising an CH_2R^4 substituted piperazine ring (closely related to the compounds excluded from the scope of D1 by proviso, cf claim 1 of D2 and example 28, 29, 31 or 32). Consequently, the document D2 prompts the skilled in the art faced with the above mentioned problem to use the compounds excluded by the proviso of D1 as lipid lowering agents. These compounds fall within the present claim 1 which, therefore, does not involve inventive activity.

Inventive activity could only be acknowledged if the claimed compounds exhibited

unexpected effects or properties in relation to the closest compounds of D1 (cf. above).